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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/777,492	EUL, JOACHIM	
	Examiner	Art Unit	
	DANA SHIN	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-65* is/are pending in the application.

4a) Of the above claim(s) *1-12,24-57,64 and 65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-23 and 58-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Sequence Rule Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

CFR §1.821(d) reads as follows:

Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims or the patent application.

In the instant case, Figures 1A, 9A, 9B, 9C,10A-10C, 12B, 13A-13B, 16A-16B, 17A-17K, 18A-18M, 19A-19E contain nucleic acid sequences which are not preceded by "SEQ ID NO:". Either the Figures themselves or the description of the drawings must contain appropriate SEQ ID NOs. See also pages 52-56 of the specification filed on October 26, 2005. Applicant is encouraged to carefully review the entire application and ensure sequence rule compliance as set forth in CFR §1.821(d).

Election/Restrictions

Applicant's election with traverse of claims 13-23 and 58-63 in the reply filed on March 25, 2008 is acknowledged. The traversal is on the ground(s) that all pending claims were indicated as searchable without effort justifying an additional fee according to the International Search Authority and therefore there is no serious search burden if restriction is not required. This is not found persuasive because the restriction requirement for the instant application was required under 35 U.S.C. §121 (U.S. practice), which is different from the PCT Rules 13.1, 13.2, and 13.3 (international practice). As such, applicant's arguments are based on non-analogous comparisons between the two entirely different restriction requirement practices.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Currently, claims 1-65 are pending. Claims 1-12, 24-57, and 64-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Accordingly, claims 13-23 and 58-63 are currently under examination on the merits.

Specification

The disclosure is objected to for containing sequence rule non-compliant subject matter. See page 2 above and the attached Notice to Comply.

Appropriate correction is required.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Germany and EP on August 13, 2001 and August 13, 2002. It is noted, however, that applicant has not filed certified copies of the "101 39 492.6" and "PCT/EP02/09082" applications as required by 35 U.S.C. 119(b). Since it is indeterminate whether the prior applications describe the claimed subject matter in the manner provided by the first paragraph of 35 USC 112, the instant filing date of February 12, 2004 will be the effective filing date for clams 13-23 and 58-63.

Claim Objections

Claim 58 is objected to because of the following informalities: Line 1 recites, "A probe RNA-encoding DNA for th e RNA-encoding DNA". It appears that applicant meant to write the word "the" instead of "th e" as underlined. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14-23 recite the limitation "The repair RNA-encoding DNA according to claim 13" in line 1. There is insufficient antecedent basis for this limitation in the claim, because claim

13 recites a "trans-splicing RNA-encoding DNA", not the "repair RNA-encoding DNA". Further, claim 13 does not contain any claim language pertinent to the meaning of "repair".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 13-17, 19, 21-22, 58-60, and 62-63 are rejected under 35 U.S.C. 102(b) and 102(a) as being anticipated by Mitchell (US 6,013,487).

Note that the claims will remain rejected under 102(a) in the event that the foreign priority to the German application is granted in the instant case.

The claims are drawn to a DNA construct that encodes a trans-splicing RNA, wherein the DNA construct comprises nucleotide sequences encoding a replication origin, an RNA polymerase-II promoter, a polyadenylation sequence, at least one antisense sequence hybridizing with at least 18 nucleotides in the mutated exon or a flanking intron region, the 5' outron antisense sequence having a branch A site of the 8-mer sequence hybridizes with the intronic polypyrimidine sequence of U and C and an AG dinucleotide at the 3' splice site and a GU

dinucleotide and a 3-mer sequence of "AAG" at the 5' splice site, wherein the construct further comprises a cDNA sequence of non-mutated exon 1, and a probe comprising the DNA construct wherein the probe lacks the ATG sequence and has the 6-mer sequence of "GUAAGU".

Mitchell teaches a DNA construct that encodes a trans-splicing RNA, comprising a polyadenylation sequence, polypyrimidine tract, branch A site, 3' splice site comprising an AG dinucleotide and a 5' splice site comprising "GUAAGU", a 15-30 nucleotide sequence complementary to (or in antisense orientation) the targeted region of the selected pre-mRNA including exon 1 lacking the ATG sequence, or an entire coding sequence of the pre-mRNA, which produces a therapeutic molecule in a cell when the DNA construct is introduced into the cell. See Figures 4A and 6B; columns 2, 4-7; claims 19-34. Mitchell teaches that the DNA construct that produces said therapeutic molecule in a cell is a commercially available vector pcDNA3.1(-), which comprises CMV promoter, T7 promoter, multiple cloning site, BGH polyadenylation sequence, f1 origin, neomycin resistant gene (ORF), SV40 early polyadenylation signal, pUC origin, and ampilicin resistance gene. See columns 8-18 and the attached citation. Accordingly, all claim limitations are taught by Mitchell.

Claims 13-15 and 58 are rejected under 35 U.S.C. 102(e) as being anticipated by Sullenger et al. (US 6,897,016 B1).

The claims are described above.

Sullenger et al. teach an expression vector comprising a trans-splicing RNA molecule such as a ribozyme or an antisense oligonucleotide that range from 10-500 nucleotides in length and is complementary to the target pre-mRNA sequence, wherein the expression vector repairs mutations in a given gene when introduced into a cell. See columns 2-16; claims 1-5. Since it is

an inherent property of an expression vector to comprise a polymerase II promoter, a polyadenylation signal sequence, and a replication origin, as evidenced by pcDNA3.1 of Invitrogen (see the attached citation), the expression vector encoding a trans-splicing RNA molecule of Sullenger et al. meets all the structural limitations set forth in the claims, absent evidence to the contrary.

Claims 13-15, 21-22, 58-60, and 62 are rejected under 35 U.S.C. 102(b) as being anticipated by Puttaraju et al. (*Nature Biotechnology,* 1999, 17:246-252).

The claims are described above.

Puttaraju et al. teach a trans-splicing DNA construct comprising an 18-nucleotide target binding domain sequence that is complementary to a target pre-mRNA sequence, a branch point sequence having a "UACUAAC" consensus sequence, a polypyrimidine tract sequence, and an AG dinucleoitde at the 3' splice site, wherein all sequences are cloned into pcDNA3.1,. which inherently has a polymerase II promoter and a polyadenylation signal sequence. See the attached Promega citation. They teach that the trans-splicing DNA construct is useful in RNA repair. Note that the trans-splicing DNA construct of Puttaraju et al. meets all of the structural limitations of the probes of claims 58-60 ad 62. Accordingly, all claim limitations are taught by Puttaraju et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-23 and 58-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Puttaraju et al. as applied to claims 13-15 and 58-60 above, and further in view of Reyes et al. (*RNA,* 1996, 2:213-225), Caudevilla et al. (*Nucleic Acids Research,* 2001, 19:3108-3115), and Bruzik et al. (*PNAS,* 1995, 92:7056-7059).

The claims are drawn to a DNA construct that encodes a trans-splicing RNA, wherein the DNA construct comprises nucleotide sequences encoding a replication origin, an RNA polymerase-II promoter, a polyadenylation sequence, at least one antisense sequence hybridizing with at least 18 nucleotides in the mutated exon or a flanking intron region, the 5' outron antisense sequence having a branch A site of the 8-mer sequence of "UACUAACA/G" hybridizes with the intronic polypyrimidine sequence of U and C and an AG dinucleotide at the 3' splice site and a GU dinucleotide and a 3-mer sequence of "AAG" at the 5' splice site, wherein the construct further comprises a cDNA sequence of non-mutated exon 1 and an ESE sequence, and a probe comprising said DNA construct.

Puttaraju et al. teach a trans-splicing DNA construct comprising an 18-nucleotide target binding domain sequence that is complementary to a target pre-mRNA sequence, a branch point sequence having a "UACUAAC" consensus sequence, a polypyrimidine tract sequence, and an AG dinucleoitde at the 3' splice site, wherein all sequences are cloned into pcDNA3.1,. which inherently has a polymerase II promoter and a polyadenylation signal sequence. See the attached Promega citation. They teach that the trans-splicing DNA construct is useful in RNA repair. See the entire reference. Puttaraju et al. do not teach that the trans-splicing DNA construct comprises

an GU dinucleotide at the 5' splice site, or the 5' splice site has the 6-mer sequence of "GUAAGU", or at least one ESE sequence.

Reyes et al. teach that the "GU" dinucleotide is the canonical 5' splice site recognition sequence during trans-splicing and that the 5' splice site comprises a sequence of GUAAGU. See the entire reference.

Caudevilla et al. teach that an ESE (exonic splicing enhancer) sequence induces or activates trans-splicing. See the entire reference.

Bruzik et al. teach that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. See the entire reference.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the trans-splicing DNA construct of Puttaraju et al. so that it further comprises the 5' splice site sequence of Reyes et al. and the ESE sequence of Caudevilla et al.

One of ordinary skill in the art would have been motivated to combine the trans-splicing factors of Reyes et al. and Caudevilla et al. with a reasonable expectation of success, because Bruzik et al. taught that trans-splicing is mediated by interactions between splicing factors bound to the splicing enhancer sequence and general splicing factors bound to the 5' and 3' splice sites. Hence, one of ordinary skill in the art trying to enhance the trans-splicing efficacy of the trans-splicing DNA construct capable of gene repair such as the trans-splicing DNA construct of Puttaraju et al. would have been motivated to incorporate the 5' splice site sequence as well as the ESE sequence into the trans-splicing DNA construct. Since the trans-splicing elements claimed in the instant case were known to not only exist but also to cooperatively orchestrate the trans-splicing activity of a trans-splicing RNA at the time of the invention, and since the skills

and knowledge to make the claimed trans-splicing construct were within the technical grasp of one of ordinary skill in the art as shown by Puttaraju et al., the claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANA SHIN whose telephone number is (571)272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

/J. E. Angell/
Primary Examiner, Art Unit 1635